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Clinical characteristics and risk factors of drug-induced lung injury by ALK tyrosine kinase inhibitors: A single center retrospective analysis

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Keywords
Alectinib; anaplastic lymphoma kinase; ceritinib; crizotinib; drug-related side effects and adverse reactions.

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Abstract

Background: If anaplastic lymphoma kinase (ALK) gene rearrangement in lung cancer is identified, ALK-tyrosine kinase inhibitors (ALK-TKIs) can be an effective treatment. However, the details of drug-induced lung injury (DILI) caused by ALK-TKI, which can be a serious side effect of ALK-TKIs, remains unclear. This study aimed to investigate the clinical features and the onset risk factors of DILI by ALK-TKIs in clinical practice.

Methods: The clinical features of 56 consecutive patients who received crizotinib, alectinib, and/or ceritinib at our hospital from 2012 to 2018 were retrospectively examined. Among these, patients diagnosed with DILI due to ALK-TKIs were evaluated in terms of clinical features and parameters. Each clinical parameter before the administration of ALK-TKIs was compared between the DILI onset group and the non-onset group.

Results: A total of seven cases were diagnosed with DILI due to ALK-TKIs; no DILI-related deaths were observed. Chest computed tomography (CT) scan findings identified six patients with the organizing pneumonia (OP) pattern and one with the hypersensitivity pneumonia pattern. The onset of DILI was significantly different in patients age ≥ 64 years and with a creatinine clearance <80 mL/minute.

Conclusions: Extra caution for DILI due to ALK-TKIs may be needed when recommending ALK-TKIs for patients over 64 years of age, or with decreased renal function. CT images of the majority of patients with DILI by ALK-TKIs show an OP pattern.

Key points

- Significant findings of the study: Extra caution is needed when recommending ALK-TKIs for patients over 64 years of age or those with decreased renal function. Computed tomography images of the majority of patients with DILI by ALK-TKIs show an OP pattern.
- What this study adds: The same or a different ALK-TKI may be considered as a treatment option after the onset of DILI, based on careful judgment.

Introduction

Anaplastic lymphoma kinase (ALK) gene rearrangements are found in approximately 2.4%–5.6% of patients with non-small cell lung cancer (NSCLC) who show a distinct clinical course with substantial antitumor response to oral tyrosine kinase inhibitors targeting ALK.[1,2] Since tyrosine kinase activity is present in the ALK protein, the effect is obtained by inhibiting this activity.[3] To date, four different ALK-tyrosine kinase inhibitors (ALK-TKIs), crizotinib, alectinib, ceritinib and lorlatinib have been used in clinical practice for the treatment of advanced ALK positive lung cancer in Japan. However, ALK-TKIs are known to potentially cause serious adverse events (SAEs), including lung injury.

ALK-TKI-induced lung injury was first reported in Japanese patients treated with crizotinib for metastatic NSCLC.[4] Subsequently, sporadic cases were reported[5,6] indicating that ALK inhibitor-induced pneumonitis can be clinically problematic in some patients. Although re-administration of another ALK-TKI after ALK-TKI-induced interstitial lung disease seems possible and has been reported in previous studies,[7,8] there have been few reports regarding the detailed clinical course after drug-induced lung injury (DILI), or readministration of ALK-TKIs. According to the results of all case surveys by pharmaceutical companies, the incidence rate of lung injury was 2.6%–5.9%, and the mortality rate was 0%–19% for the three ALK-TKIs.[9,10] On the other hand, a recent systematic review and meta-analysis of the incidence of ALK inhibitor-related pneumonitis in patients with advanced NSCLC indicated a slightly lower global incident rate (2.1%). This report also suggested a higher incidence of ALK inhibitor-induced pneumonitis in cohorts from Japan (6.3%) when compared to cohorts from other countries (1.1%).[11] However, the information of ALK-TKI-induced lung injury in the clinical practice remains limited.

The purpose of this study was to investigate the clinical features, risk factors, and the safety of readministration of ALK-TKIs after ALK-TKI-induced lung injury.

Methods

In accordance with the amended Declaration of Helsinki, we conducted a single-center, retrospective study for ALK-TKI-induced lung injury. All procedures involving human participants were approved by the Human Ethics Committee of the Graduate School of Medicine of Chiba University (approval number 2265). Approval for the opt-out consent method was given by the Chiba University Hospital.

Patients

The records of 56 consecutive patients with ALK positive lung cancer who were treated with crizotinib, alectinib, and/or ceritinib from August 2012 to August 2018 at our hospital were retrospectively examined. Crizotinib, alectinib, and ceritinib were administered to 23, 25, and eight patients, respectively. Patients treated with lorlatinib were not included as lorlatinib was not available at the time of the present study in Japan. Among the 56 patients, cases diagnosed with DILI due to ALK-TKIs were evaluated with regard to their clinical features, risk factors, and recurrence after treatment of DILI with ALK-TKIs. Each clinical parameter before administration of an ALK-TKI was also compared between the DILI onset group and the non-onset group (Figure S1). Patients for whom multiple ALK-TKIs had been used were included as different cases according to the type of ALK-TKI they received. A total of 11 patients who switched to alectinib from crizotinib, seven patients who switched to ceritinib from alectinib, two patients who switched to crizotinib from alectinib, and one patient who switched to ceritinib from crizotinib due to the disease progression or side effects were included in the total of 56 patients. There were no patients who had a prior history of having received radiotherapy.

Diagnosis of ALK-TKI-induced lung injury

Drug-induced lung injury was diagnosed using the following diagnostic criteria:[12] (i) patients with a treatment history of ALK-TKI; (ii) clinical manifestations reported to be induced by the corresponding drug; (iii) exclusion of other causes of clinical manifestations; (iv) improvement after drug discontinuation; and (v) exacerbation by re-administration. Two physicians individually confirmed the final diagnosis of DILI.

Evaluation of parameters and clinical progression

Data regarding clinical progression, blood test findings, and chest computed tomography (CT) scan findings for the 56 patients were retrieved from their medical records. We analyzed the presence of pulmonary metastasis, history and comorbidity of interstitial pneumonia, histologic lung cancer type, and smoking history. We evaluated laboratory data included the estimated creatinine clearance (Ccr), lactate dehydrogenase (LDH) levels, white blood cell (WBC) and eosinophil counts, Krebs von den Lungen-6 (KL-6; normal range, <500 U/mL) protein levels, brain natriuretic peptide (BNP; normal range, <18.4 pg./mL) levels, percentage of predicted vital capacity, and forced expired volume in one second/forced vital capacity. Clinical course after

the onset of DILI (eg, response to cessation of drug or steroid, status of improved, stable, etc) was also evaluated.

Chest CT data analysis

Based on the official American Thoracic Society/European Respiratory Society statement and The Japanese Respiratory Society Guidelines for the Management of Drug-induced Lung Disease 2018,[13,14] the CT pattern-organizing pneumonia (OP), diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP), or hypersensitivity pneumonia (HP) for each patient was determined. Additionally, patients' course (ie, improved, unchanged, worsened) were also evaluated. In periodical follow-up CT scan for lung cancer, conventional 5 mm slice CT was basically performed for all patients. A 0.5 or 1 mm slice chest high-resolution computed tomography (HRCT) scan was reperformed on three patients at the onset of DILI.

Statistical analysis

Clinical data are expressed as means ± standard deviation (SD). All statistical analyses were conducted using the JMP Pro 13.2.0 (Japanese version, SAS Institute Inc). We considered a *P*-value of <0.05 to be statistically significant. Odds ratios and 95% confidence intervals (CI) for DILI onset were evaluated using univariate analyses. We defined the different patient categories according to the number of risk factors observed to be related to DILI onset. We used the Cochran-Armitage trend test to evaluate the relation between the number of risk factors and DILI onset and the Kaplan-Meier method to estimate the time to DILI onset for each subgroup stratified by the number of risk factors.

Results

Baseline characteristics of total cases, DILI- and non-DILI groups

A total of seven (two men and five women) of the 56 (12.5%) patients were diagnosed with DILI (crizotinib, $n = 1$; alectinib, n = 5; ceritinib, $n = 1$). The baseline characteristics in all cases are shown in Table 1. There were no significant differences between the DILI and non-DILI groups with regard to sex, smoking history, LDH, KL-6, BNP levels, whereas significant differences were noted with regard to age ≥ 64 years and Ccr < 80 mL/min at baseline obtained by ROC analysis. The two groups showed no significant differences in baseline chest CT findings, including the presence of pulmonary metastasis and interstitial changes (Table 2).

From these results, two patient-related risk factors, age ≥ 64 years and Ccr < 80 mL/min, were identified as significantly related to DILI onset. The number of risk factors and their relation to the frequency of DILI onset are summarized in Figure 1. The number of risk factors was significantly associated with DILI onset; DILI onset was not seen in patients with no patient-related risk factors, while 26.3% of patients who had both risk factors experienced DILI onset. The progress to DILI onset according to the number of risk factors is significantly different between patients with no risk factors and patients with one or two risk factors (Fig 1).

Characteristics of cases at DILI onset

The characteristics of patients at DILI onset are shown in Table 3. Five cases were diagnosed with DILI at the time of routine follow-up chest CT, and two cases were diagnosed with DILI using CT to evaluate the appearance of shadows on chest radiographs after dyspnea and/or slight fever. The CT images of each patient were separately evaluated by two physicians. Bronchoscopy was performed in three patients and the results were all consistent with DILI: the finding of interstitial pneumonia in pathological diagnosis (Case A); the finding of epithelioid granulomas in pathological diagnosis (Case C); the finding of organizing pneumonia in pathological diagnosis; and a high percentage of lymphocytes in bronchoalveolar lavage (Case D). The median time from the start of ALK-TKI administration to the onset of DILI was 97 days (range: 9–531 days). We observed one case of grade 2 pneumonitis due to DILI with crizotinib. For alectinib, we observed one case of grade 1, three cases of grade 2, and one case of grade 4 pneumonitis due to DILI. Only one case of grade 2 pneumonitis was observed due to DILI with ceritinib. Each ALK-TKI type usually resulted in a grade 2 pneumonitis.

CT pattern of cases at DILI onset

The CT patterns of patients at DILI onset are shown in Table 3. Six (85.7%) patients exhibited the OP pattern, one (14.3%) exhibited the HP pattern, and one (14.3%) exhibited the NSIP pattern. Figures 2 and 3 show the plain CT images of the seven patients.

Outcome after DILI onset

Of the seven patients with DILI, one exhibited an improvement on follow-up with no intervention and without discontinuation of an ALK-TKI of alectinib (Case E), one exhibited an improvement with systemic corticosteroid therapy, and four exhibited improvement with systemic corticosteroid therapy and ALK-TKI discontinuation (Table 3). One patient (Case F) did not recover. The primary cause of death in Case F was considered to be

Table 1 Baseline characteristics of total patients

	Total (n = 56)	DILI group (n = 7)	Non-DILI group (n = 49)
Age (years)	59.5 ± 12.9	71.2 ± 5.8	57.8 ± 12.8
Male/female	26/30	2/5	24/25
Smoking history, n (%)	23 (41.0%)	2 (28.5%)	21 (42.8%)
Histologic type			
Adenocarcinoma, n (%)	54 (96.4%)	7 (100%)	46 (95.9%)
Squamous cell carcinoma, n (%)	1 (1.7%)	0 (0%)	1 (2.0%)
Other, n (%)	1 (1.7%)	0 (0%)	1 (2.0%)
Lung metastasis, n (%)	43 (76.7%)	6 (85.7%)	37 (75.5%)
Pre-existing ILD, n (%)	10 (17.8%)	1 (1.4%)	9 (18.3%)
Laboratory findings			
LDH (IU/L)	265.9 ± 150.9	336.1 ± 292.0	255.8 ± 120.9
Ccr (mL/min)	82.9 ± 31.5	60.4 ± 21.5	86.1 ± 31.6
KL-6 (U/mL)	979 ± 1004	1038 ± 1215	966 ± 993
	(n = 23)	(n = 4)	(n = 19)
BNP (pg/mL)	25.5 ± 21.3	26.5 ± 8.5	25.2 ± 23.5
	(n = 21)	(n = 4)	(n = 17)
WBC (/μL)	7141 ± 3336	9228 ± 6349	6842 ± 2644
Eosinophils/WBC (%)	2.4 ± 1.8	2.1 ± 2.3	2.4 ± 1.8
Spirometry			
%VC	81.7 ± 17.7	89.9 ± 23.7	80.0 ± 16.5
	(n = 23)	(n = 4)	(n = 19)
FEV_1/FVC	76.7 ± 7.5	73.1 ± 7.7	77.4 ± 7.1
	(n = 23)	(n = 4)	(n = 19)

Data are expressed as mean ± standard deviation. %VC, percent vital capacity; BNP, brain natriuretic peptide; Ccr, creatinine clearance; DILI, drug-induced lung injury; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; WBC, white blood cells.

progression of lung cancer. An ALK-TKI was re-administered in the five patients after improvement of DILI, of which three had no relapse of DILI. Cases A and B were the cases where different ALK-TKIs had been used in the same patient. The patient continued treatment with ALK-TKI after the onset of the DILI. With regard to the clinical course of the patient who had a DILI relapse (the first DILI was due to alectinib, the second DILI was due to ceritinib; Fig 2), the treatment of the patient with the first DILI due to alectinib was changed to treatment with ceritinib. Then, the second DILI was observed in chest CT scan 110 days after using ceritinib, but subsequently improved with corticosteroid therapy. The DILI resulted in discontinuation of ceritinib. Ceritinib was changed to a cytotoxic agent and no further DILI was observed. The two cases of DILI recurrence showed improvement with systemic corticosteroid treatment (Table S1).

Discussion

In the present study, we investigated the clinical characteristics of ALK-TKI-induced lung injury and found that age ≥ 64 years and Ccr < 80 mL/min at baseline may be risk factors. In most cases with ALK-TKI-induced lung injury, an OP pattern on chest CT scan was observed at DILI onset; the therapeutic response to corticosteroid therapy was then relatively good.

Patients age ≥ 64 years was a significantly different factor between the DILI group and non-DILI group; in addition, Ccr < 80 mL/min before ALK-TKI administration was also significantly different. The post-marketing survey of crizotinib has suggested that the risk factors for DILI include old age, performance status of Eastern Cooperative Oncology Group ≥2, existing interstitial pneumonia, or history of interstitial pneumonia, existing pleural effusion, and a history of smoking.[9] In a previous retrospective review of interstitial lung disease (ILD) associated with crizotinib therapy, a greater percentage of ex-smokers were shown in the patients with crizotinib-related ILD.[15] One of the ways in which this study was different from the previous literature might be that the present study targeted multiple ALK-TKI drugs and not just a single one (eg, crizotinib).

A total of 12.5% patients (7 of 56 patients) in the present study were diagnosed with DILI, and the median time from ALK-TKI administration to DILI onset was 97 days (range: 9–531 days). Suh *et al.* conducted a systematic review and meta-analysis which reported that the global incident rate of ALK inhibitor-related pneumonitis in patients with advanced NSCLC was 2.1%.[11] We considered that the higher incidence rate in this study (n = 7/56,

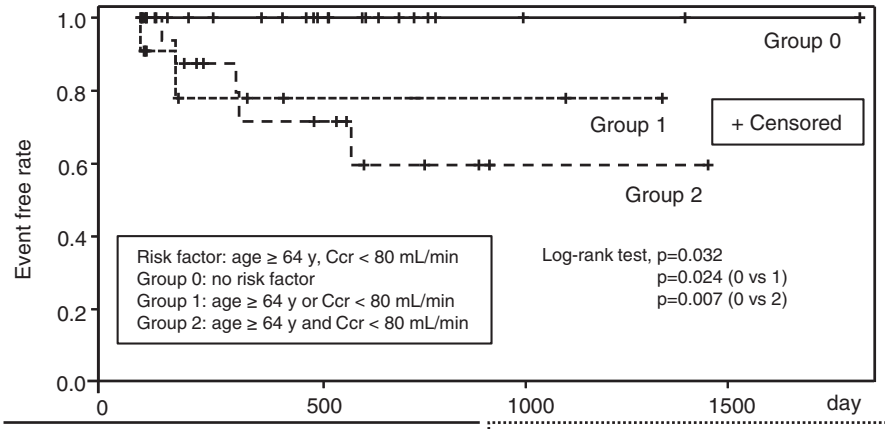
Table 2 Risk factors associated with DILI onset due to ALK-TKIs

Factors	*n* (*n* = 56)	DILI onset (*n* = 7)	Univariate analysis	
			OR (95% CI)	*P*-value
Sex				
M	30	2	1	
F	26	5	2.40 (0.47–17.89)	0.30
Age				
Continuous value			1.11 (1.03–1.22)	0.01
<64	34	1	1	
≥64	22	6	12.38 (1.90–244.18)	0.01
Smoking history				
Current + Ex	23	2	1	
Non-smoker	33	5	1.88 (0.36–13.99)	0.46
Lung metastasis				
Nonexistent	13	1	1	
Existent	43	6	1.95 (0.29–38.66)	0.53
Pre-existing ILD				
Existent	10	1	1	
Nonexistent	46	6	1.35 (0.20–27.13)	0.79
LDH (IU/L)				
Continuous value			1.00 (1.00–1.01)	0.25
<230	31	3	1	
≥230	25	4	1.78(0.36–9.84)	0.48
Ccr (mL/min)				
Continuous value			0.96 (0.92–1.00)	0.02
≥80	29	1	1	
<80	27	6	8.00 (1.24–157.11)	0.03
KL-6 (U/mL)				
Continuous value			1.00 (1.00–1.00)	0.90
<500	12	2	1	
≥500	11	2	1.11 (0.11–10.91)	0.92
BNP (pg/mL)				
Continuous value			1.00 (0.94–1.05)	0.92
<18.4	10	1	1	
≥18.4	11	3	3.38 (0.35–76.18)	0.30

ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor; BNP, brain natriuretic peptide; Ccr, creatinine clearance; DILI, drug-induced lung injury; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase.

12.5%) was attributed to the population difference (Japanese) and our study design (ie, a retrospective study for a small number of cases with various comorbidities and therapeutic course, and the readministration of ALK-TKI after the onset of DILI due to another ALK-TKI). In particular, the incidence of ILD by alectinib which was mainly administered in our study was differently reported in two phase III studies with a similar design comparing alectinib with crizotinib.[16,17] The incidence of alectinib-induced ILD was 8% (n = 8/103) in J-ALEX conducted exclusively in Japan[16] and 1% (n = 2/152) in ALEX study not including Japan.[17] In the subanalysis in the systematic review and meta-analysis by Suh *et al.*[11] also suggested the incidence of ALK inhibitor-induced pneumonitis in cohorts from Japan were higher (6.3%) when compared to cohorts from other countries (1.1%).[11]

In general clinical practice, drugs suspected to cause DILI should not be re-administered. However, resuming ALK-TKIs after resolution of a lung injury might be a clinical option because ALK-TKIs have a potent antitumor effect. In fact, some studies have reported successful readministration of a different ALK-TKI after the occurrence of DILI.[7,8] In the present study, ALK-TKIs were again successfully administered to three patients after the resolution of DILI. In addition, the relapse of ALK-TKI DILI after the initial resolution of DILI was improved in two patients with treatment (Cases A and G). In Case A, the first DILI due to alectinib was improved when corticosteroids and alectinib were discontinued. After the resolution of the first DILI due to alectinib, Case A was switched to ceritinib to treat their lung cancer. A DILI recurrence was subsequently recognized, but it was also improved by



Number of Risk factors	n	DILI onset n	DILI onset %	*p*-value*
0	26	0	0.0	
1	11	2	18.2	0.007
2	19	5	26.3	

	No. of Patients	Event	Censored
Group 0	26	0	26
1	11	2	9
2	19	5	14

Figure 1 Kaplan-Meier plot of time to DILI onset classified according to the number of risk factors. Solid, dotted, and dashed lines correspond to zero (in 26 patients), one (in 11 patients), and two (in 19 patients) risk factors. *Categorical data analysis conducted using the Cochran-Armitage trend test.

Table 3 The characteristics of patients at DILI onset

Case	ALK-TKI	Onset (day)	Previous treatment	History of DILI by ALK-TKI	Image pattern	Grade	Treatment for DILI	Outcome
A	Alectinib	531	Crizotinib	–	OP	2	Alectinib discontinuation and PSL	Improvement
B	Ceritinib	97	Alectinib	+	OP	2	Ceritinib discontinuation and PSL	Improvement
C	Alectinib	97	Crizotinib	–	HP	2	PSL	Improvement
D	Alectinib	246	Crizotinib	–	OP + NSIP	2	Alectinib discontinuation and PSL	Improvement
E	Alectinib	254	Crizotinib	–	OP	1	Alectinib continuation	Improvement
F	Alectinib	9	No	–	OP	4	Alectinib discontinuation and PSL	No improvement (death from lung cancer)
G	Crizotinib	63	No	–	OP	2	Crizotinib discontinuation and PSL	Improvement

DILI, drug-induced lung injury; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor; OP, organizing pneumonia; PSL, prednisolone; HP, hypersensitivity pneumonia; NSIP, nonspecific interstitial pneumonia.

corticosteroid and ceritinib discontinuation. In Case G, the first DILI due to crizotinib was improved by corticosteroid and crizotinib discontinuation. After the resolution of the first DILI due to crizotinib, Case G again received crizotinib with a dose reduction, and under treatment with corticosteroid. The DILI recurrence was recognized, but it was improved after crizotinib discontinuation. With regard to the response to corticosteroid therapy in the present study, among the six patients with improved DILI, five improved with corticosteroid therapy and one was relieved only after the cessation of ALK-TKI.

In this study, the CT patterns of patients at the onset of DILI were mainly OP patterns. On the other hand, in a previous retrospective review of CT images in patients with EGFR-TKI-induced interstitial lung disease, the DAD pattern was most commonly observed.[18] Approximately one third of cases of DILI as a result of EGFR-TKIs are fatal with DAD appearance on chest CT scan.[19,20] For DILI-induced by ALK-TKIs in the present study, improvements were observed in almost all cases. When the same or a different ALK-TKI was administered after the improvement of the first DILI following administration of ALK-TKI, some patients did not show a recurrence of DILI, and some patients who showed a recurrence of DILI subsequently improved with corticosteroid therapy (Table S1). From these results, even if DILI is diagnosed, the prognosis of DILI after administration of ALK-TKIs may be better than that by EGFR-TKIs. One of the possible reasons might be

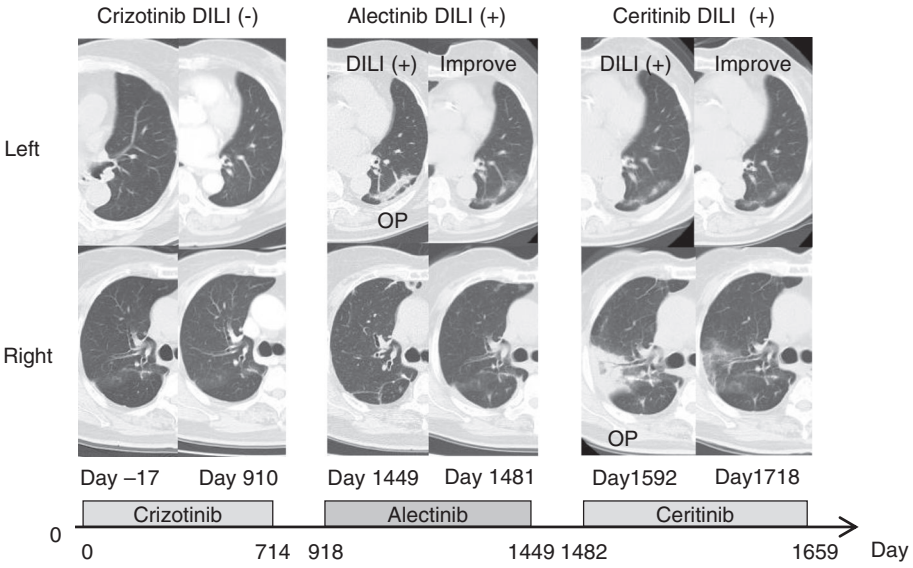


Figure 2 Clinical course of two re-administration cases. A 70-year-old woman with advanced ALK-positive non-small cell lung cancer (NSCLC) was treated with crizotinib as second-line chemotherapy. DILI was not observed during crizotinib administration, but progress of cancer was recognized. Therefore, alectinib was administered to the patient as third-line chemotherapy (Case A). DILI was observed during alectinib administration (day 531), and improved with steroid therapy and discontinuation of alectinib. Re-administration of ALK-TKI was with ceritinib (Case B). There was onset of DILI upon administration of ceritinib (day 97). DILI improved with discontinuation of ceritinib and with steroid therapy.

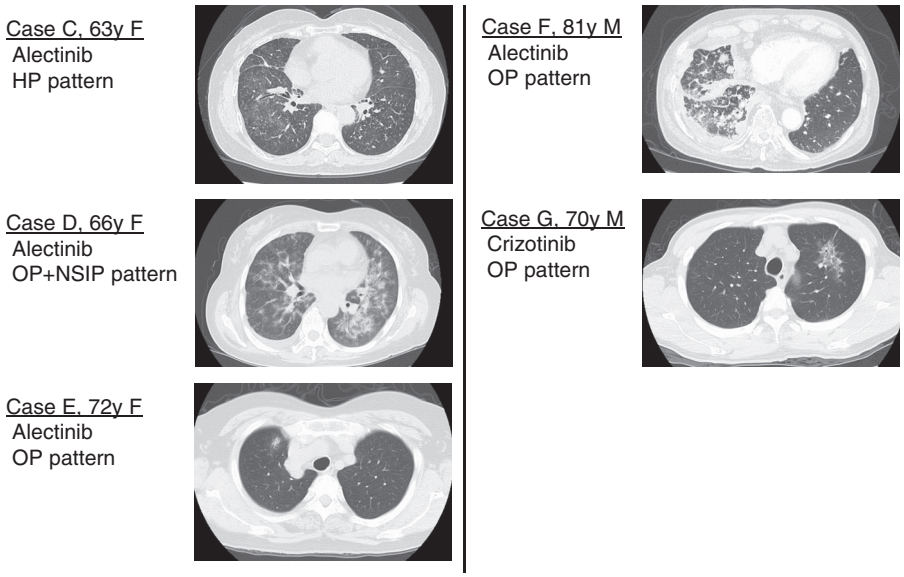


Figure 3 Computed tomography (CT) findings at the onset of DILI. Computed tomography findings in five cases with ALK-TKI-induced drug injury. Case C, hypersensitivity pneumonia pattern; Case D, organizing pneumonia (OP) + nonspecific interstitial pneumonia pattern; Case E, OP pattern; Case F, OP pattern; Case G, OP pattern.

that the DAD pattern in DILI by ALK-TKI is uncommon. Therefore, we considered that treatment continuation may be one of our options under careful observation or in future issues to be considered.

This study had several limitations. First, it was designed as a retrospective, single-center study. Second, the sample size was small, which was also why univariate and not multivariate logistic regression analysis was chosen. Third, DILI was primarily diagnosed based on conventional CT findings. DILI in asymptomatic patients could have been overlooked because the timing of CT was at the discretion of the physician, and we included not only HRCT but also conventional CT data in the study. Since ALK-TKI-induced lung injury is reportedly a relatively rare condition (2.1%–6.3%) and the number of ALK-TKI administered cases in this study were quite small, it is difficult to accurately describe the clinical implications. However, we believe that it is important to elucidate the underlying condition in order to accurately reflect a clinical outcome, even with a small number of cases, and assist in assembly of the total number of reported cases.

In conclusion, our results suggest that patients age ≥ 64 years and with Ccr < 80 mL/min at baseline may be at an increased risk of DILI by ALK-TKIs. Extra caution may be needed when recommending ALK-TKIs for patients who meet these criteria, although the treatment response appears to be good. The same or a different ALK-TKI may be considered as a treatment option after DILI

onset, based on careful judgment because DILI might not recur, or the treatment response might be relatively good, even if it does recur. Readministration of ALK-TKI is one of the issues that requires resolution as it is currently not definitive and there are only a few reported cases in the literature.

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Disclosure

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

APPENDIX S1. Supporting information

